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[Claim(s)]
[Claim 1] The HIV cofactor inhibitor characterized by containing the oligonucleotide which includes a complementary base sequence to the base sequence of CXCR4 gene or CCR5 gene.
[Claim 2] The HIV cofactor inhibitor according to claim 2 which is the oligonucleotide in which the aforementioned oligonucleotide has the base sequence expressed with the arrangement of the arrangement number 1 of an arrangement table - the arrangement number 119.
[Claim 3] The HIV cofactor inhibitor according to claim 1 or 2 whose at least one interchange nucleotide binding of the aforementioned oligonucleotide is phosphorothioate type combination.
[Claim 4] A HIV cofactor inhibitor given in Claim 1 - any 1 clause of three which contain a stable liposome further in blood.
[Claim 5] The HIV cofactor inhibitor according to claim 4 said whose liposome is a liposome formed from lipid system polymer or amino acid nature polymer.
[Claim 6] The HIV cofactor inhibitor according to claim 5 which is the membrane fusion type with which said liposome consists of a complex of lipid system polymer or amino acid nature polymer, and a viral-envelope protein or its fragment.
[Claim 7] The HIV cofactor inhibitor characterized by containing ** KUTA which contains the oligonucleotide of a description in Claim 1 - any 1 clause of three.
[Claim 8] The HIV cofactor inhibitor according to claim 7 said whose vector is non-fecundity adenovirus ** KUTA or a non-fecundity retroviral vector.

[Detailed Description of the Invention]
[0001]
[Field of the Invention] This invention relates to a HIV cofactor inhibitor. The HIV cofactor inhibitor by this invention can be used for prophylaxis against HIV infection and/or a HIV infection therapy as an anti-HIV agent.
[0002]
[Description of the Prior Art] a virus is the microbe of the shape of a particle which consists of nucleic acid of either DNA or RNA, and a small number of protein molecule -- it -- if independent, it cannot increase, but it can invade into a Homo sapiens host cell, and can increase for the first time using a host's

metabolic system. Generally, in a Homo sapiens host cell, a virus takes the process of adsorption, invasion, uncoating, transfer, an assembly, germination, and discharge, and increases. As an "antivirotic" to such a virus, various antibiotics have been used from the former. For example, by checking the stage where an influenza virus invades into a cell, amantadine is shown and an antiviral action [a nucleoside system antivirotic (for example, ara-A)] Since by checking the duplicate (synthesis) of nucleic acid shows an antiviral action, neither can say it as a desirable antivirotic in that a Homo sapiens host cell is affected.

[0003] It is desirable to have the operation which stops multiplication of a virus as an antivirotic to the virus which makes representation a human immunodeficiency virus (it is hereafter called HIV for short) without affecting a Homo sapiens host cell. However, when virus multiplication arises within a host cell, the most is dependent on the metabolism and the function in a host cell. For this reason, if in charge of development of a desirable antivirotic, the fundamental knowledge about multiplication of each virus must be accumulated. According to such a situation, development of the antivirotic which does not affect a Homo sapiens host cell is behind very much compared with development of an antibiotic.

[0004] It succeeded in decreasing the viral RNA concentration in blood below to a detection limit as a HIV therapeutic drug in recent years by 3 agent combined therapy which combined a HIV protease inhibitor and two kinds of conventional HIV reverse transcriptase inhibitor. For this reason, when showing the symptoms of an acquired immunode-ficiency syndrome, it is being considered to be curable illness from the incurable illness considered that it cannot but wait for death. However, the problem of the tolerance virus appearance according [the aforementioned 3 agent combined therapy] to a side reaction or chronic administration etc. is not solved.

[0005] HIV-1 is roughly classified into three kinds according to the kind of cell with which it can be infected. that is, CD4+ A T-lymph cell T-lymph cell directivity (T-tropic) HIV-1;CD4+ which cannot be infected with a macrophage although it can be infected with a cultivation T-lymph cell stock Macrophage directivity which cannot be infected with a cultivation T-lymph cell stock although it can be infected with a T-lymph cell and a macrophage (M-tropic) They are three kinds of both directivity (dual-tropic) HIV-1 which can be infected with HIV-1; and any cell. On the other hand although CD tetrad was reported as a receptor used when HIV-1 invades into a target cell in the next year of 1983 (1984) when HIV-1 was discovered Invasion of HIV-1 found that a second receptor (a co-receptor or cofactor) other than CD4 was also required. [that the second receptor of T-lymph cell directivity HIV-1 is CXCR4 (CXC chemokine receptor 4)] It was reported by Berger and others in 1996 [Feng, Y.et al., Science, 272,872-977 (1996)]. That is, when the cell of the mouse which made CD4 receptor which is a receptor of HIV-1 discover was made to discover CXCR4, T-lymph cell directivity HIV-1 was infected with said cell, but infection of macrophage directivity HIV-1 was not materialized. On the other hand, even if it made the cell which does not discover CD4 receptor discover only CXCR4, HIV-1 was not infected.

[0006] Moreover, CXCR4 from next month of a report [Dragic, T.etal. and Nature as which the paper about the second receptor of macrophage directivity HIV-1 was announced successively, 381,667-673 (1996);Doranz, B.et al, Cell, 85, 1149-1158 ; (1996) Deng, H.et al., Nature, 381,661-666(1996); Alknatib, G.et al., Science, 272, 1955-1958(1996); and Choe, and H.et al., Cell, 85, 1135-1148(1996)].

[0007] According to these reports, [the second receptor of macrophage directivity HIV-1] three sorts of CC chemokines -- [-- that is, [RANTES and (regulated-upon-activation, normal T expressed and secreted)] It is the receptor of MIP(macrophage inflammatrory protein)-1alpha or MIP-2beta], and it

turned out that CCR5 (cc chemokine receptor 5) are main.
[0008] As mentioned above, it became clear by having identified the second receptor of different HIV-1 of cell directivity, respectively to depend for the determination of cell directivity of HIV-1 on the second receptor use ability of each viral strain. namely, [the cultivation T-lymph cell stock which has discovered only CXCR4] T-lymph cell directivity HIV-1 can be infected, macrophage directivity HIV-1 can be infected with the macrophage monocyte which has discovered only CCR5, and any virus can be infected with the CD4+ T-lymph cell which has discovered both receptors. And, of course, both directivity HIV-1 can be infected with any cell.
[0009] As a result, the following three methods are examined as approach of an acquired immunodeficiency syndrome therapy. The 1st is the method of using low-molecular antagonist. Although it is not low-molecular, the report that the analog (antagonist) of RANTES controls infection of macrophage directivity HIV-1 specifically is actually made. In addition to using competition with a low-molecular agonist and HIV-1, the 2nd has a method of using the down regulation of the chemokine receptor by a low-molecular agonist. However, this method is not given to the level of the applied research. Although the 3rd is the method of using the chemokine itself which is the ligand of a second receptor, it worries about strong toxicity. Thus, the present condition is that the effective cure for a true meaning cannot say by the analog of RANTES although a certain amount of HIV-1 prevention of transmission is expectable.
[0010] The antisense method which makes a gene a target as an antivirotic of HIV with an intense variation on the other hand is effective. The antisense method is technology which checks translation in transfer of a target gene, splicing, and/or protein, and controls the manifestation of virus protein specifically using the oligonucleotide which has a complementary base sequence to a target gene. One of the most important technical problems is selection of a target site in development of such an antisense method. In addition, although the second receptor of different HIV-1 of cell directivity was identified, respectively, the cell directivity of HIV-1 was not necessarily solved completely. For example, it can be infected with the cell which discovered CCR5 artificially also on the initial HIV-1 isolation stock (primary HIV-1 isolate) which cannot be infected with a macrophage. It is thought that the factor which there is also a report that CXCR4 are discovered and determines cell directivity also on a macrophage is still more complicated. Therefore, of course, it cannot be easily assumed whether a means effective in the prevention of transmission or the therapy of HIV is offered by the antisense method which uses a second receptor as a target gene. Furthermore, it is never easy to choose an effective target field from the gene which carries out the code of the second receptor.
[0011]
[Problem to be solved by the invention] The result of this invention person having made it the technical problem to develop the effective antisense method to HIV, and having inquired wholeheartedly, Antisense oligo NUREOCHIDO to the specific target field of CCR5 gene which is the second receptor of the macrophage directivity HIV, or the specific target field of CXCR4 gene which is the second receptor of the T-lymph cell directivity HIV found out checking infection of HIV. This invention is based on such knowledge.
[0012]
[Means for solving problem] Therefore, this invention relates to the HIV cofactor inhibitor characterized by containing the oligonucleotide which includes a complementary base sequence to the base sequence of CXCR4 gene or CCR5 gene.
[0013] In this Description, "HIV" means a human immunodeficiency virus (human immunodeficiency

virus) and HIV-1 and its variant are included. Moreover, in this Description ["cofactor / HIV"] The second receptor (namely, co-receptor) of HIV is meant, and CXCR4 (CXC chemokine receptor 4) and CCR5 (cc chemokinereceptor 5) are included. a group called a 7 times film penetration type G-protein conjugate receptor in CXCR4 and CCR5 -- [it is a receptor belonging to a chemokine receptor family, and CXCR4] It is the second receptor of the T-lymph cell directivity HIV, and CCR5 are the second receptor of the macrophage directivity HIV. Furthermore, in this Description, a "gene" means the field transferred by mRNA, i.e., the field from a transcription initiation site to a terminator.

[0014]

[Mode for carrying out the invention] The oligonucleotide used in the HIV cofactor inhibitor of this invention makes a target field all the fields of CXCR4 gene or CC-CCR5 gene, i.e., the field from a transcription initiation site to a terminator, and includes a complementary base sequence to the base sequence of the target field. As said target field, the field by the side of 5' is desirable among all the fields of CXCR4 gene or CC-CCR5 gene, the field to 1/2 of a transcription initiation site - all the fields is more desirable, and it is desirable that it is especially a field containing the translation initiation codon ATG.

[0015] Although the number of bases in particular of the oligonucleotide used in the HIV cofactor inhibitor of this invention is not limited, it is desirable that it is more than the number of bases that can be hybridized specifically to the aforementioned target field, and it is desirable that it is below the number of bases that can pass a cell membrane and a nuclear membrane. 15 or more bases of the numbers of bases which can be hybridized are 20 or more bases more preferably specifically to the aforementioned target field. Moreover, in order to guarantee membrane permeability, 30 or less bases are 28 or less bases more preferably. Therefore, the oligonucleotide used by this invention consists of 15 to 28 base more preferably 15 to 30 base. As long as it can combine with the target field (for example, mRNA) specifically and a double chain can be formed in the oligonucleotide used by this invention it is not necessary to include a complementary base sequence continuously to a target field -- the non-complementary base 1 or more than it -- the part beyond 1 or it -- deletion -- you may be inserted and/or replaced. However, the oligonucleotide which includes a complementary base sequence continuously to a target field is desirable.

[0016] The concrete base sequence of the oligonucleotide used by this invention can be suitably determined according to the mold of HIV made into a target. For example, to the macrophage directivity HIV based on the base sequence of CCR5 gene Or to the T-lymph cell directivity HIV, a target base sequence and the number of bases can be determined from a viewpoint of stable double chain formation based on the base sequence of CXCR4 gene, and an antisense oligonucleotide can be compounded by a well-known method.

[0017] In the oligonucleotide used in the HIV cofactor inhibitor of this invention, the interchange nucleotide binding between each nucleoside is a phosphodiester bond or a modification phosphodiester bond independently, respectively. Methyl phosphonate combination which replaced one oxygen atom of the two non-bridging oxygen atoms of a phosphodiester bond by the methyl group as a modification phosphodiester bond, for example, one oxygen atom of the two non-bridging oxygen atoms of a phosphodiester bond -- an amino group -- it replaced by the substituted amino group youthfully -- [it together and] [phosphoroamidite-] Or phosphorothioate type combination which replaced one oxygen atom of the two non-bridging oxygen atoms of a phosphodiester bond by the sulfur atom can be mentioned, and more than those one sort or they can be introduced into one place or the part beyond it of

com ination between nucleosides. As an oligonucleotide used in this invention [points /, such as arra gement specific binding nature, the simple method of preparation, and synthetic cost,] It is desi able that it is a phosphodiester bond object, and it is desirable that it is the phosphodiester bond obje t embellished from points, such as double chain stability, anti-nuclease tolerance, cell membrane perr eability and low cytotoxic effect, and metabolic [moderate]. Since stability in the living body is goo , it is desirable that it is especially phosphorothioate type combination.

[00 3] [the oligonucleotide used in this invention] Each base which constitutes the base sequence of eac gene of CCR5 which are a target gene, i.e., the second receptor of HIV, or CXCR4, That is, T (thy ine) or U (uracil), C, G, and A can be used for A (adenine), G (guanine), C (cytosine), and T (thy ine) as a complementary base, respectively. When the oligonucleotide used in this invention is RN , U is used for A which constitutes the base sequence of CCR5 or CXCR4 gene as a com olementary base.

[00 9] The oligonucleotide used in this invention can be formed from a guanine deoxyriboside, ribo ucleosides, and/or those modification nucleosides, for example, a 2'-O-modification ribonucleoside, as l ng as it can combine with a target field specifically and a double chain can be formed. As a mo fication ribonucleoside, the point of the strength of avidity with the base sequence which serves as a ta get to a 2'-O-methyl ribonucleoside is desirable. [therefore, the oligonucleotide used in this inv ition] The oligo ribonucleotide (RNA) which consists of a ribonucleoside and/or a modification ribo ucleoside, The oligodeoxyribonucleotide (DNA) which consists only of a deoxyribonucleoside, Or the can be chimera cage GORIBO / deoxyribonucleotide (RNA/DNA) which consists of both a ribo ucleoside (and/or, modification ribonucleoside) and a deoxyribonucleoside.

[00 0] As an oligonucleotide used in this invention, the following oligonucleotides can be mentioned cor rete, for example. namely, as an oligonucleotide which includes a complementary base sequence to the ase sequence of CCR5 gene It has the base sequence expressed with the arrangement of the arra gement number 1 of an arrangement table - the arrangement number 63. It has the base sequence as the ase sequence expressed with the arrangement of the arrangement number 1 of oligonucleotide; or an rrangement table - the arrangement number 63 which is a phosphodiester bond with all the same inte change nucleotide bindings. More than one place or it of an interchange nucleotide binding (pr erably all) can mention the oligonucleotide which is phosphorothioate type combination. moreover, as a oligonucleotide which includes a complementary base sequence to the base sequence of CXCR4 ger It has the base sequence expressed with the arrangement of the arrangement number 64 of an arr gement table - the arrangement number 119. It has the base sequence as the base sequence exp essed with the arrangement of the arrangement number 64 of oligonucleotide; or an arrangement tab - the arrangement number 119 which is a phosphodiester bond with all the same interchange nuc eotide bindings. More than one place or it of an interchange nucleotide binding (preferably all) can me tion the oligonucleotide which is phosphorothioate type combination. All these oligonucleotides are eff ctive to HIV (especially HIV-1) respectively.

[0(1] The oligonucleotide used in this invention is compoundable by a well-known method. If the part wh ch introduces a 2'-O-methyl ribonucleotide or phosphorothioate combination is removed For exa mple, it is compoundable using the DNA/RNA automatic synthesis machine by the phosphodiester me od, a usual phospho triester method, for example, the H-phosphonate method, or the usual ph sphoroamidite method.

[0(2] [the oligonucleotide which has a 2'-O-methyl ribonucleotide] For example, it is compoundable

using the DNA/RNA automatic synthesis machine by the phosphoroamidite method using a 5'-dimethoxy triethyl 2 '-O-methyl ribonucleoside 3'-[(2-cyano ethyl)-(N and N-diisopropyl)]-phosphoroamidite unit. [the oligonucleotide which has phosphorothioate combination] For example, 15% of N, N, N', and N'-tetraethyl thio ram disulfide / acetonitrile solution can be used and compounded instead of the water / iodine / pyridine solution which is the oxidizing agent used for the usual polynucleotide synthesis.

[0023] The liposome which can be used in this invention will not be restricted especially if stable in blood. Here, when an animal is medicated with the HIV cofactor inhibitor of this invention, saying "are stabilized in blood", it is not losing the transfer capability until an oligonucleotide is transported to an animal cell. And this stability contacts the HIV cofactor inhibitor and animal serum of this invention for 24 t 72 hours, for example. After incubating at 27 degrees C, it can know by investigating the incorporation capability of the oligonucleotide to the animal cell concerned about what added the animal cell or incubated similarly three persons of a HIV cofactor inhibitor, animal serum, and an animal cell. The liposome which can be used by this invention is a liposome prepared from lipid system polymer (for example, lipid molecules, such as phospholipid, a glycolipid, or cholesterol) or amino acid nature polymer, for example, and either an one-sheet film liposome or its multilamellar liposome is effective. Moreover, in this invention, the well-known membrane fusion type liposome which consists of a complex of lipid system polymer or amino acid nature polymer, and a viral-envelope protein (especially HIV envelope protein) or its fragment can also be used.

[0024] As phospholipid which can prepare a liposome general -- a glycerophospholipid (phosphatidylcholine and phosphatidylethanolamine --) Phosphatidylserine, phosphatidic acid, phosphatidylglycerol, Phosphatidylinositol, KARUJI opine, or a sphingophospholipid (a sphingomyelin, ceramide phosphoryl ethanolamine, or ceramide phosphoryl glycerol) can be mentioned. Moreover, as a glycolipid which can prepare a liposome, a glycoglycerolipid (digalactosyl diglyceride or seminolipid) or a sphingoglycolipid (galactosylceramide or lactosylceramide) can be mentioned, for example. As amino acid nature polymer which can prepare a liposome, poly-L-lysine or Polly L- (lysine/serine) can be mentioned, for example.

[0025] A commercial liposome can also be used in this invention. As a commercial item which can be used by this invention For example, Genetransfer[N-(alpha-trimethylammonio acetyl) dodecyl D-GURUTA mate clo RISHIDO, The mixture of] which consists of composition of L-alpha-phosphatidylethanolamine dioleoyl and a L-alpha-phosphatidylcholine JIRAU reel of 1:2:3, and HMG-1 and 2 (Wako Pure Chem), N, N, N', an N '- tetramethyl N and N'-screw (2-hydroxyethyl)-2, 3-dioleoyl oxy-1, the liposome formed from the mixture of 4-butane dianmonium iodide and L-dioleoyl phosphatidylethanolamine (Tfx-10; pro mega company), It is formed from the mixture (52:40:8) of L-alpha-dipalmitoylphosphatidylcholine, cholesterol, and stearyl amine. It is formed from the mixture (54:40:6) of the liposome (coat SOMU EL-C-01; Nippon Oil & Fats Co., Ltd.) which has positive charge or L-alpha-dipalmitoylphosphatidylcholine, cholesterol, and L-alpha-dipalmitoyl phosphatidylglycerol. The liposome (coat SOMU EL-N-01; Nippon Oil & Fats Co., Ltd.) which has a weak negative charge can be mentioned. Although a liposome has a neutral liposome, a negative charge liposome, a ****** liposome, pH susceptibility liposome, etc. according to the status of the charge of a polar part, a negative charge liposome or a ****** liposome is desirable.

[0026] In this invention, as a desirable liposome especially N, N, N', and N -- '- tetramethyl N and N' -- the liposome (Tfx-10) formed from the mixture of - bis(2-hydroxyethyl)-2, 3-dioleoyl oxy-1, and 4-

butane JIAMMONIU iodide and L-dioleoyl phosphatidylethanolamine -- or The liposome formed from a mixture with L-alpha-dipalmitoylphosphatidylcholine, cholesterol, stearyl amine, or L-alpha-dipalmitoyl phosphatidylglycerol, It is especially formed from the mixture (52:40:8) of L-alpha-dipalmitoylphosphatidylcholine, cholesterol, and stearyl amine. It is formed from the mixture (54:40:6) of the liposome (coat SOMU EL-C-01) which has positive charge or L-alpha-dipalmitoylphosphatidylcholine, cholesterol, and L-alpha-dipalmitoyl phosphatidylglycerol. The liposome (coat SOMU EL-N-01) which has a weak negative charge can be mentioned.

[0027] In the HIV cofactor inhibitor by this invention, if said oligonucleotide and the liposome stable in blood contain simultaneously in containing the aforementioned oligonucleotide and a liposome stable in blood simultaneously, those existence forms in particular will not be limited. For example, it can be the form of the mixture of the aforementioned oligonucleotide and a liposome or a complex (complex), the embedding object of the oligonucleotide by a liposome, or a capsulation thing. The aforementioned complex is the method of using an oligonucleotide and a liposome as a complex using an electrostastic combination, i.e., the method called the RIPOFE cushion method, can mix both slowly in a test tube, and can prepare them by neglecting it for about 15 minutes in a room temperature grade, for example. The aforementioned embedding object can be prepared by the method of making an oligonucleotide the form enclosed in the liposome, for example. That is, using lipids, such as phosphatidylserine, the liposome of a multiplex layer is prepared with a vortex mixer etc., next it sonicates and the liposome of an one-sheet film is prepared. After adding an oligonucleotide to the obtained one-sheet film liposome and applying to a vortex mixer etc. lightly, it can prepare by incubating for about 10 minutes at about 37 degrees C, or freeze-drying and rehydrating. The aforementioned capsulation thing can also be prepared by a well-known method.

[0028] As a vector which can be used in this invention, the well-known vector for gene therapies can be mentioned, for example. About the well-known vector for gene therapies, for example The 12th volume of the experimental medicine of history ****** of Takaku (special number number), It is indicated to No 15 "front line of gene therapy" (1994). For example, a retroviral vector, an adenovirus vector, an adenovirus company (associated) virus, a herpesvirus vector, a vaccinia virus vector, poxvirus, or a bacterial plasmid can be mentioned. It is desirable to use a non-fecundity retroviral vector or a non-fecundity adenovirus vector at the point which is a point of the singularity to a target cell, or can be introduced into a cell efficient.

[0029] The HIV cofactor inhibitor of this invention can be prescribed for the patient according to taking orally or a parenteral or local pathway. Although a dose changes depending on dosage forms and administration time, an interval, etc. of the response of the individual to the kind of the animal for a therapy (mammals, especially Homo sapiens), and its drugs, and the tablet chosen, generally it can be prescribed for the patient by the dosage of the range of about 5000g/day from about 500mg. The HIV cofactor inhibitor of this invention The aforementioned oligonucleotide, A medicine can be prescribed for the patient according to taking orally or a parenteral or local pathway at a single time or two or more times in combination with a well-known carrier or a well-known diluent permissible [with a case] in physic in addition to the vector which contains a stable liposome and/or said oligonucleotide in blood. The dosage forms with which the HIV cofactor inhibitor of this invention differs in versatility For example, it can be made a tablet, a capsule, a lozenge agent, the trochiscus, a hard candy, powders, spray, cream pharmaceuticals, an ointment, suppositories, jellies, gel, a paste agent, lotions, an ointment, the mixture, the solution agent for injection, elixirs, syrups, etc.

[00)]
[Function] [the operation by the HIV cofactor inhibitor of this invention] , for example if said antisense oligonucleotide borrows the help (for example, a liposome or a vector) of cell membrane permeability sthenia of a cell introduction agent etc. and reaches in an infected cell although not limited to the following reasoning When mRNA and the antisense oligonucleotide of CXCR4 or CC-CCR5 join together, the manifestation of CXCR4 which are the second receptor of HIV, or CC-CCR5 is controlled, and. as a result, it is thought that infection of HIV is checked. Therefore, the antivirotic effect can also be synergistically heightened for said antisense oligonucleotide to HIV a single time or by carrying out continuous administration into a vein, combining a cell introduction agent.
[00 1]
[Working example] Hereafter, although a work example explains this invention concretely, these do not limit the range of this invention.
[A work example 1] <<Design of an antisense oligonucleotide>> in order to use it in the following work examples (1) It has a complementary base sequence to the base sequence of CCR5 gene. Below 63 kinds of antisense oligonucleotide [all the interchange nucleotide bindings of whose are phosphorothioate type combination "Oligonucleotide AS(s)-1" It has a complementary base sequence to the base sequence of]; called - "oligonucleotide AS(s)-63" and (2) CXCR4 gene. All the interchange nucleotide bindings designed 56 kinds of antisense oligonucleotides ["oligonucleotide AS(s)-64" - "oligonucleotide AS(s)-119 is called hereafter] which are phosphorothioate type combination.
[00 2] Moreover, it has some base sequences of (3) CCR5 gene as an oligonucleotide for comparison. Below 1 kind of sense oligonucleotide [all the interchange nucleotide bindings of whose are phosphorothioate type combination]; called "Oligonucleotide SE (s)" and (4) All the interchange nucleotide bindings are phosphorothioate type combination, and one kind of scramble oligonucleotide ["Oligonucleotide SC (s)" is called hereafter] to CCR5 gene was designed. [oligonucleotide / as opposed to / be / it / under / this / Description / setting / a certain gene (for example, CCR5 gene) / in addition, / a "scramble oligonucleotide"] It is the oligonucleotide compounded in order to compare an effect with an antisense oligonucleotide or a sense oligonucleotide. each base (A --) which constitutes the antisense oligonucleotide or sense oligonucleotide used as the candidate for comparison It consists of a base of the same number as the number of bases of G, C, and T, and what has the base sequence moreover designed so that the portion of said gene (for example, CCR5 gene) throat might not form a double chain is meant.
[00 3] In the term of each aforementioned oligonucleotide designed by this example, it means that "AS" is an antisense oligonucleotide, means that "SE" is a sense oligonucleotide, and means that "SC" is a scramble oligonucleotide. Moreover, "(s)" means that all the interchange nucleotide bindings are phosphorothioate type combination (a phosphorothioate type may be called hereafter).
[00 4] "Oligonucleotide AS(s)-1" which is a phosphorothioate type oligonucleotide - "oligonucleotide AS(s)-63", the base sequence of "Oligonucleotide SE (s)" and "Oligonucleotide SC (s)" -- drawing 1 and drawing 2 -- and "Oligonucleotide AS(s)-64" which is a phosphorothioate type oligonucleotide The base sequence of - "oligonucleotide AS(s)-119" is shown in drawing 3 and drawing 4 , respectively. "A", "G", "C and "T" express adenine, guanine, a cytosine, and a thymine, respectively during the arrangement of each oligonucleotide shown in drawing 1 - drawing 4 .
[00 5]
[A work example 2] <<Synthesis of an oligonucleotide>> The oligonucleotide designed in the work

example 1 was compounded using the program for phosphorothioate type oligonucleotides according to the procedure shown below with the DNA automatic synthesis machine (model 392: applied bio-systems company). Namely, the solid phase column (British KURUAKEMU) and DNA synthesis reagent (British KURUAKEMU) of a 1micromol scale are used. It compounded by the phosphoroamidite method and deprotection was hereafter carried out from the column according to the conventional method (A.Chollet and E.H.Kawashima, Nucleic Acids Res., and [13, 1529] (1985)). Electrophoresis of the 1/500 quantity (about 4microg) of the obtained oligonucleotide was carried out using the 20% polyacrylamide gel containing 7M urea. Electrophoresis was performed on the fixed voltage of 150V for 1.5 hours. The methylene blue stain was performed after the end of electrophoresis, and it checked that each synthetic oligonucleotide was the purpose chain length.

[0055] The 20% polyacrylamide gel electrophoresis (for logging refining) which contains 7M urea again was presented with 1/5 to 1 of the obtained oligonucleotide / 2 quantity (about 1.2mg) about each oligonucleotide by which it was checked that he is the target chain length. Electrophoresis was carried out on the fixed voltage of 200V for 6 hours. After removing from the gel board after the end of electrophoresis and wrapping in a wrap film, ultraviolet rays were irradiated and the mark was put on the purpose chain length's band. With the disinfected cutter knife, the gel inside the mark was started and it brought together in the 1.5ml sample inner tube. Added 0.4ml of 10 mM-Tris-HCl (pH 7.5) buffer solution containing 1 mM-EDTA to the started gel, it was made to vibrate at 37 degrees C for several hours, and DNA to solution was extracted from the piece of a gel. DNA extract was collected, a phenol / chloro form extraction was performed, and acrylamide removal and DNA refining were performed by operating ethanol precipitation further. Each yield was 0.3-0.6mg. By the polyacrylamide containing 7M urea electrophoresis of the degree of refining of the obtained oligonucleotide (about 0.5microg) was carried out, and it was checked.

[0057]

[Work example 3] <<Evaluation test in the prevention of transmission of the macrophage directivity HIV >> In this example, the following examinations were done for the purpose of evaluating the preventive effect of an antisense oligonucleotide over macrophage directivity HIV infection. As a cell with which HIV is infected, the COS cell (A41 cell is called hereafter) which discovers both CD4 receptor and CCR5 was used. In a medium, moreover, 10% serum (Fetal Calf Serum;JRH BIOSCIENCES6H2162), 500microg/ml-G418 sulfate (sulfate) (GENETICIN; Gibco Lot No.77K7566), And the DMEM medium (the medium for cultivation is called hereafter) containing 200microg [/ml] hygromycin B (Boehringer Mannheim;Lot No.843555) was used.

[0058] First, the various oligonucleotides adjusted to various concentration using said medium for cultivation were added to A41 cell adjusted [ml] in 100,000 pieces /. As said oligonucleotide, "oligonucleotide AS(s)-1" - "oligonucleotide AS(s)-63" compounded in said work example 2, "Oligonucleotide SE (s)", and "Oligonucleotide SC (s)" were used. After the cell culture for five days, A4 cell was readjusted [ml] in 100,000 pieces /, and was cultured for further 24 hours. m.o. It added to 200micro of macrophage directivity HIV infection cell strain JR-CSF stock lA41 cell, and cultivated for 4 hours so that i. might be set to 0.01. After washing a virus by a DMEM medium, A41 cell which carried out virus infection was cultured for eight days. And the cultivated cell supernatant was measured with the ELISA kit (first chemistry HIV-p24 kit; first chemicals industrial Lot No.DIC-240805) of p24, and the effect of each oligonucleotide was computed from the result.

[0059] The result of oligonucleotide AS(s)-1 which is the active substance of this invention is combined

with the result of the oligonucleotide SE (s) which is an oligonucleotide for comparison, and is shown in drawing 5 . In addition, the control shown in drawing 5 shows the result in oligonucleotide additive-free (botn [namely,] an antisense oligonucleotide a sense oligonucleotide and a scramble oligonucleotide additive-free). As opposed to a phosphorothioate type sense oligonucleotide [SE (s)] having hardly controlled virus infection The phosphorothioate type antisense oligonucleotide [AS(s)-1] showed the depressor effect of virus infection also in low concentration (1microM), and controlled virus infection 90% or more by the concentration of 5microM. Also in another phosphorothioate type antisense oligonucleotide [AS(s)-2 - AS(s)-63] although the same virus infection depressor effect was shown Compared with AS(s)-37 - AS(s)-63, the trend for depressor effect to become high in the direction of AS (s)- - AS(s)-36 was observed, and the trend for the depressor effect of AS(s)-1 - AS(s)-18 to become still nigher also in it was observed.

[0040]

[A work example 4] <<Evaluation test in the infection therapy of the macrophage directivity HIV>> In this example, the following examinations were done for the purpose of evaluating the curative effect of the antisense oligonucleotide to macrophage directivity HIV infection. First, it cultivated for 24 hours, after adding the macrophage directivity HIV infection cell strain JR-CSF stock adjusted so that m.o.i. mignt be set to 0.01 to A41 cell adjusted [ml] in 100,000 pieces /. After washing a superfluous virus by the medium for cultivation, the various oligonucleotides adjusted to various concentration using the medium for cultivation were added to A41 cell with which a virus was infected. As said oligonucleotide, the various oligonucleotides used in the work example 3 were used. Three days and six days after oligonucleotide addition, A41 cell was readjusted [ml] in 100,000 pieces /, and cultivation was continued. Eight days after oligonucleotide addition, cell supernatants were collected and ELISA measurement was performed like said work example 3.

[0041] The result of oligonucleotide AS(s)-1 which is the active substance of this invention is shown in drawing 6 . In addition, the control shown in drawing 6 shows the result in oligonucleotide additive-free (botn [namely,] an antisense oligonucleotide a sense oligonucleotide and a scramble oligonucleotide additive-free). The phosphorothioate type antisense oligonucleotide controlled a little more than about 50% of virus infection also low concentration (1microM). Also in another phosphorothioate type antisense oligonucleotide [AS(s)-2 - AS(s)-63] although the same virus infection depressor effect was shown Compared with AS(s)-37 - AS(s)-63, the trend for depressor effect to become high in the direction of AS(s)-1 - AS(s)-36 was observed, and the trend for the depressor effect of AS(s)-1 - AS(s)-18 to become still higher also in it was observed.

[0042]

[A work example 5] <<Evaluation test in the prevention of transmission of the T-lymph cell directivity HIV >> In this example, the following examinations were done for the purpose of evaluating the preventive effect of an antisense oligonucleotide over T-lymph cell directivity HIV infection. Namely, the thing for which the COS cell which discovers both CD4 receptor and CXCR4 was used instead of A2_ cell given in a work example 3 as a cell with which HIV is infected; as a HIV infection cell strain using [for the work example 3]-instead of macrophage directivity HIV infection cell strain JR-CSF stock of description-four to three shares of T-lymph cell directivity HIV infection cell strains NL; -- and The procedure of the description was repeated in the work example 3 except having used as an oligonucleotide oligonucleotide AS(s)-64 compounded in said work example 2 - oligonucleotide AS(s)-11 [the oligonucleotide] although the phosphorothioate type antisense oligonucleotide [AS(s)-64 - AS

(s)- 9] showed sufficient depressor effect in virus infection Compared with AS(s)-85 - AS(s)-119, the tren for depressor effect to become high in the direction of AS(s)-64 - AS(s)-84 was observed, and the tren for the depressor effect of AS(s)-64 - AS(s)-68 to become still higher also in it was observed.
[00 3]
[A ork example 6] <<Evaluation test in the infection therapy of the T-lymph cell directivity HIV>> In this xample, the following examinations were done for the purpose of evaluating the curative effect of the ntisense oligonucleotide to T-lymph cell directivity HIV infection. Namely, the thing for which the CO cell which discovers both CD4 receptor and CXCR4 was used instead of A22 cell given in a work exa ple 4 as a cell with which HIV is infected; as a HIV infection cell strain using [for the work exa ple 4]-instead of macrophage directivity HIV infection cell strain JR-CSF stock of description-four to t ee shares of T-lymph cell directivity HIV infection cell strains NL; -- and The procedure of the des iption was repeated in the work example 4 except having used as an oligonucleotide olig nucleotide AS(s)-64 compounded in said work example 2 - oligonucleotide AS(s)-119. [the olig nucleotide] although the phosphorothioate type antisense oligonucleotide [AS(s)-64 - AS(s)-119] sho ed sufficient depressor effect in virus infection Compared with AS(s)-85 - AS(s)-119, the trend for dep essor effect to become high in the direction of AS(s)-64 - AS(s)-84 was observed, and the trend for the epressor effect of AS(s)-64 - AS(s)-68 to become still higher also in it was observed.
[00 4]
[Ef ct of the Invention] The HIV cofactor inhibitor of this invention can perform effective prevention or a effective therapy to infection of HIV by using a specific antisense oligonucleotide. Moreover, acc rding to advance with sick HIV, the cell directivity changes and the T-lymph cell directivity HIV is mai ly detected for the macrophage directivity HIV from a patient in the infection last stage in early sta s of infection. Since the manifestation of two kinds of HIV cofactors (CCR5 and CXCR4) can be con olled separately, respectively according to the HIV cofactor inhibitor of invention, it is possible to per rm the more suitable therapy according to the stage of infection.
[00 5]
[La out Table]
[00 6]
arr igement number: -- length [of 1 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid seq ence GATAATGGAT CTTGTTCCCA 20 [0047]
arr igement number: -- length [of 2 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid seq ence GATTGGACTT GACACTTGTA 20 [0048]
arr igement number: -- length [of 3 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid seq ence TAATAATTGA TGTCATAGGA 20 [0049]
arr igement number: -- length [of 4 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid seq ence GGCAGGGCTC CGATGTATAA 20 [0050]
arr igement number: -- length [of 5 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid seq ence CTTCACATTG ATTTTTTGGC 20 [0051]
arr igement number: -- length [of 6 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid seq ence AGGCGGGCTG CGATTTGCTT 20 [0052]
arr igement number: -- length [of 7 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid seq ence GAGTGAGCGG AGGCAGGAGG 20 [0053]
arr igement number: -- length [of 8 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid

sequence CAAAGATGAA CACCAGTGAG 20 [0054]
arrangement number: -- length [of 9 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence CATGTTGCCC ACAAAACCAA 20 [0055]
arrangement number: -- length [of 10 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence AGGATGAGGA TGACCAGCAT 20 [0056]
arrangement number: -- length [of 11 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence CGGAAAACGT CAAATAGTCC 20 [0057]
arrangement number: -- length [of 12 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence CAGTCAGTAC GAGAAGTCGG 20 [0058]
arrangement number: -- length [of 13 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence AGGTTGAGCA GGTAGATGTC 20 [0059]
arrangement number: -- length [of 14 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence ACAGGTCAGA GATGGCCAGG 20 [0060]
arrangement number: -- length [of 15 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence GGGGACAGTA AGAAGGAAAA 20 [0061]
arrangement number: -- length [of 16 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence GCATAGTGAG CCCAGAAGGG 20 [0062]
arrangement number: -- length [of 17 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence AGTCCCAGTG GGCGGCAGCA 20 [0063]
arrangement number: -- length [of 18 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence ACACATTGTA TTTCCAAAGT 20 [0064]
arrangement number: -- length [of 19 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence AGCCCTGTCA AGAGTTGACA 20 [0065]
arrangement number: -- length [of 20 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence AGAAGCCTAT AAAATAGAGA 20 [0066]
arrangement number: -- length [of 21 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence GAAGAAGATT CCAGAGAAGA 20 [0067]
arrangement number: -- length [of 22 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence ATTGTCAGGA GGTAGATGAA 20 [0068]
arrangement number: -- length [of 23 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence CAGCCAGGTA CCTATCGATT 20 [0069]
arrangement number: -- length [of 24 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence CACAGCATGG ACGACAGTCA 20 [0070]
arrangement number: -- length [of 25 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence CTGGATTTTA AAGCAAACAC 20 [0071]
arrangement number: -- length [of 26 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence CCCCAAAGGT GACCGTCCTG 20 [0072]
arrangement number: -- length [of 27 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence GATCACACTT GTCACCACCC 20 [0073]
arrangement number: -- length [of 28 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence ACAGCCACCA CCGAAGTGAT 20 [0074]
arrangement number: -- length [of 29 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence CTGGGAGAGG AGACGCAAAC 20 [0075]

arrangement number: -- length [of 30 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid sequence TCTGGTAAAG ATGTATCCTG 20 [0076]
arrangement number: -- length [of 31 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid sequence AGACCTTCTT TTTGAGATCT 20 [0077]
arrangement number: -- length [of 32 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid sequence AGCTGCAGGT GTAATGAAGA 20 [0078]
arrangement number: -- length [of 33 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid sequence ACTGTATGGA AAATGAGAGC 20 [0079]
arrangement number: -- length [of 34 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid sequence TTCCAGAATT GATACTGACT 20 [0080]
arrangement number: -- length [of 35 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid sequence TTAATGTCTG GAAATTCTTC 20 [0081]
arrangement number: -- length [of 36 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid sequence CCCCAAGATG ACTATCTTTA 20 [0082]
arrangement number: -- length [of 37 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid sequence AGCAGCGGCA GGACCAGCCC 20 [0083]
arrangement number: -- length [of 38 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid sequence AGCAGATGAC CATGACAAGC 20 [0084]
arrangement number: -- length [of 39 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid sequence TTTTAGGATT CCCGAGTAGA 20 [0085]
arrangement number: -- length [of 40 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid sequence CGACACCGAA GCAGAGTTTT 20 [0086]
arrangement number: -- length [of 41 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid sequence GCCTCTTCTT CTCATTTCGA 20 [0087]
arrangement number: -- length [of 42 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid sequence AAGCCTCACA GCCCTGTGCC 20 [0088]
arrangement number: -- length [of 43 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid sequence AATCATGATG GTGAAGATAA 20 [0089]
arrangement number: -- length [of 44 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid sequence AGAAGAGAAA ATAAACAATC 20 [0090]
arrangement number: -- length [of 45 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid sequence AATGTTGTAG GGAGCCCAGA 20 [0091]
arrangement number: -- length [of 46 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid sequence GTGTTCAGGA GAAGGACAAT 20 [0092]
arrangement number: -- length [of 47 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid sequence CCAAAGAATT CCTGGAAGGT 20 [0093]
arrangement number: -- length [of 48 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid sequence TCCAACCTGT TAGAGCTACT 20 [0094]
arrangement number: -- length [of 49 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid sequence TCCAACCTGT TAGAGCTACT 20 [0095]
arrangement number: -- length [of 50 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid sequence TCACCTGCAT AGCTTGGTCC 20 [0096]
arrangement number: -- length [of 51 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid

sequence CATCCCAAGA GTCACTGTCA 20 [0097]
arrangement number: -- length [of 52 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence TTGATGCAGC AGTGCGTCAT 20 [0098]
arrangement number: -- length [of 53 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence AGGCATAGAT GATGGGGTTG 20 [0099]
arrangement number: -- length [of 54 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence GAACTTCTCC CCGACAAAGG 20 [0100]
arrangement number: -- length [of 55 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence ACTAAGAGGT ACTTTCTGAA 20 [0101]
arrangement number: -- length [of 56 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence TGTGCTTTTG GAAGAAGACT 20 [0102]
arrangement number: -- length [of 57 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence GAAGCGTTTG GCAATGTGCT 20 [0103]
arrangement number: -- length [of 58 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence AAAATAGAAC AGCATTTGCA 20 [0104]
arrangement number: -- length [of 59 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence CGGGAGCCTC TTGCTGGAAA 20 [0105]
arrangement number: -- length [of 60 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence AACTGAGCTT GCTCGCTCGG 20 [0106]
arrangement number: -- length [of 61 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence CCAGTGGATC GGGTGTAAAC 20 [0107]
arrangement number: -- length [of 62 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence CAGATATTTC CTGCTCCCCA 20 [0108]
arrangement number: -- length [of 63 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence TCCGTGTCAC AAGCCCACAG 20 [0109]
arrangement number: -- length [of 64 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence ATGGAGGGGA TCAGTATATA 20 [0110]
arrangement number: -- length [of 65 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence ATACACTTCA GATAACTACA 20 [0111]
arrangement number: -- length [of 66 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence ACACCGAGGA AATGGGCTCA 20 [0112]
arrangement number: -- length [of 67 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence TCAGGGGACT ATGACTCCAT 20 [0113]
arrangement number: -- length [of 68 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence CATGAAGGAA CCCTGTTTCC 20 [0114]
arrangement number: -- length [of 69 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence TCCGTGAAGA AAATGCTAAT 20 [0115]
arrangement number: -- length [of 70 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence AATTTCAATA AAATCTTCCT 20 [0116]
arrangement number: -- length [of 71 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence CCTGCCCACC ATCTACTCCA 20 [0117]
arrangement number: -- length [of 72 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence CCATCATCTT CTTAACTGGC 20 [0118]

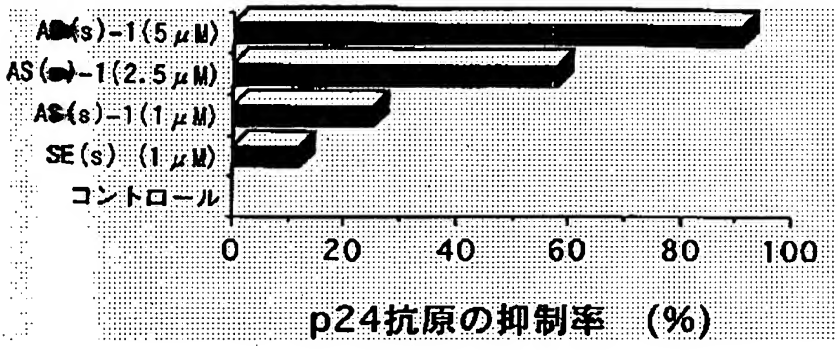
arra gement number: -- length [of 73 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequ nce GGCATTGTGG GCAATGGATT 20 [0119]
arra gement number: -- length [of 74 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequ nce ATTGGTCATC CTGGTCATGG 20 [0120]
arra gement number: -- length [of 75 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequ nce TGGGTTACCA GAAGAAACTG 20 [0121]
arra gement number: -- length [of 76 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequ nce CTGAGAAGCA TGACGGACAA 20 [0122]
arra gement number: -- length [of 77 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequ nce CAAGTACAGG CTGCACCTGT 20 [0123]
arra gement number: -- length [of 78 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequ nce TGTCAGTGGC CGACCTCCTC 20 [0124]
arra gement number: -- length [of 79 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequ nce CTCTTTGTCA TCACGCTTCC 20 [0125]
arra gement number: -- length [of 80 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequ nce TCCCTTCTGG GCAGTTGATG 20 [0126]
arra gement number: -- length [of 81 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequ nce ATGCCGTGGC AAACTGGTAC 20 [0127]
arra gement number: -- length [of 82 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequ nce TACTTTGGGA ACTTCCTATG 20 [0128]
arra gement number: -- length [of 83 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequ nce ATGCAAGGCA GTCCATGTCA 20 [0129]
arra gement number: -- length [of 84 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequ nce TCATCTACAC AGTCAACCTC 20 [0130]
arra gement number: -- length [of 85 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequ nce CTCTACAGCA GTGTCCTCAT 20 [0131]
arra gement number: -- length [of 86 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequ nce CATCCTGGCC TTCATCAGTC 20 [0132]
arra gement number: -- length [of 87 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequ nce GTCTGGACCG CTACCTGGCC 20 [0133]
arra gement number: -- length [of 88 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequ nce GCCATCGTCC ACGCCACCAA 20 [0134]
arra gement number: -- length [of 89 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequ nce CAACAGTCAG AGGCCAAGGA 20 [0135]
arra gement number: -- length [of 90 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequ nce GGAAGCTGTT GGCTGAAAAG 20 [0136]
arra gement number: -- length [of 91 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequ nce AAGGTGGTCT ATGTTGGCGT 20 [0137]
arra gement number: -- length [of 92 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequ nce CGTCTGGATC CCTGCCCTCC 20 [0138]
arra gement number: -- length [of 93 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequ nce TCCTGCTGAC TATTCCCGAC 20 [0139]
arra gement number: -- length [of 94 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid

sequence GACTTCATCT TTGCCAACGT 20 [0140]
arrangement number: -- length [of 95 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence CGTCAGTGAG GCAGATGACA 20 [0141]
arrangement number: -- length [of 96 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence ACAGATATAT CTGTGACCGC 20 [0142]
arrangement number: -- length [of 97 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence CGCTTCTACC CCAATGACTT 20 [0143]
arrangement number: -- length [of 98 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence CTTGTTGGCT GCCTTACTAC 20 [0144]
arrangement number: -- length [of 99 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence TACATTGGGA TCAGCATCGA 20 [0145]
arrangement number: -- length [of 100 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence CGACTCCTTC ATCCTCCTGG 20 [0146]
arrangement number: -- length [of 101 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence TGGAAATCAT CAAGCAAGGG 20 [0147]
arrangement number: -- length [of 102 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence GGGTGTGAGT TTGAGAACAC 20 [0148]
arrangement number: -- length [of 103 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence CACTGTGCAC AAGTGGATTT 20 [0149]
arrangement number: -- length [of 104 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence TTTCCATCAC CGAGGCCCTA 20 [0150]
arrangement number: -- length [of 105 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence CTAGCTTTCT TCCACTGTTG 20 [0151]
arrangement number: -- length [of 106 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence TTGTCTGAAC CCCATCCTCT 20 [0152]
arrangement number: -- length [of 107 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence TCTATGCTTT CCTTGGAGCC 20 [0153]
arrangement number: -- length [of 108 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence GCCAAATTTA AAACCTCTGC 20 [0154]
arrangement number: -- length [of 109 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence TGCCCAGCAC GCACTCACCT 20 [0155]
arrangement number: -- length [of 110 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence CCTCTGTGAG CAGAGGGTCC 20 [0156]
arrangement number: -- length [of 111 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence TCCAGCCTCA AGATCCTCTC 20 [0157]
arrangement number: -- length [of 112 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence CTCCAAAGGA AAGCGAGGTG 20 [0158]
arrangement number: -- length [of 113 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence GTGGACATTC ATCTGTTTCC 20 [0159]
arrangement number: -- length [of 114 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence TCCACTGAGT CTGAGTCTTC 20 [0160]
arrangement number: -- length [of 115 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid
sequence TTCAGCCTCA AGATCCTCTC 20 [0161]

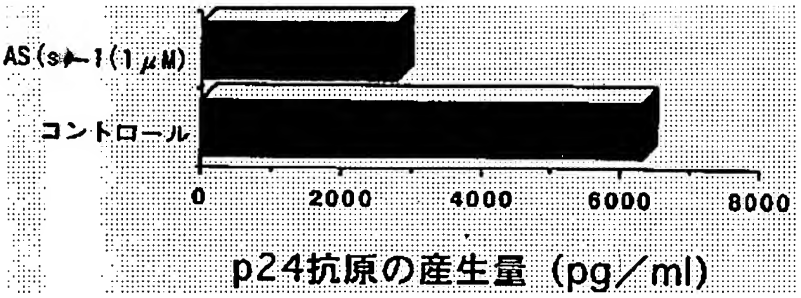
arrangement number: -- length [of 116 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid sequence CTCCAAAGGA AAGCGAGGTG 20 [0162]
arrangement number: -- length [of 117 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid sequence GTGGACATTC ATCTGTTTCC 20 [0163]
arrangement number: -- length [of 118 arrangement]: -- mold [of 20 arrangement]: -- nucleic acid sequence TCCACTGAGT CTGAGTCTTC 20 [0164]
arrangement number: -- length [of 119 arrangement]: -- mold [of 22 arrangement]: -- nucleic acid sequence TTCAAGTTTT CACTCCAGCT AA 22

[Brief Description of the Drawings]
[Drawing 1] It is the explanatory view showing the base sequence of the antisense oligonucleotide which has a complementary base sequence to the base sequence of CCR5 gene designed in the work example 1, the base sequence of the sense oligonucleotide corresponding to it, and the base sequence of a scramble oligonucleotide.
[Drawing 2] It is the explanatory view showing the base sequence of another antisense oligonucleotide which has a complementary base sequence to the base sequence of CCR5 gene designed in the work example 1.
[Drawing 3] It is the explanatory view showing the base sequence of the antisense oligonucleotide which has a complementary base sequence to the base sequence of CXCR4 gene designed in the work example 1.
[Drawing 4] It is the explanatory view showing the base sequence of another antisense oligonucleotide which has a complementary base sequence to the base sequence of CXCR4 gene designed in the work example 1.
[Drawing 5] It is the graph which shows the result of the ELISA measurement performed in the work example 3 aiming at evaluation of the prophylaxis-against-HIV-infection effect.
[Drawing 6] It is the graph which shows the result of the ELISA measurement performed in the work example 4 aiming at evaluation of a HIV infection curative effect.

[Drawing 5]



[Drawing 6]



[Drawing 1]

AS(s)-1	5′ - GAT AAT GGA TCT TGT TCC CA - 3′
SE(s)	5′ - CTA TTA GGT AGA ACA AGG TG - 3′
SC(s)	5′ - TTC CCT ATT CAA GTG ATA CT - 3′
AS(s)-2	5′ - GAT TGG ACT TGA CAC TTG TA - 3′
AS(s)-3	5′ - TAA TAA TTG ATG TCA TAG GA - 3′
AS(s)-4	5′ - GGC AGG GCT CCG ATG TAT AA - 3′
AS(s)-5	5′ - CTT CAC ATT GAT TTT TTG GC - 3′
AS(s)-6	5′ - AGG CGG GCT GCG ATT TGC TT - 3′
AS(s)-7	5′ - GAG TGA GCG GAG GCA GGA GG - 3′
AS(s)-8	5′ - CAA AGA TGA ACA CCA GTG AG - 3′
AS(s)-9	5′ - CAT GTT GCC CAC AAA ACC AA - 3′
AS(s)-10	5′ - AGG ATG AGG ATG ACC AGC AT - 3′
AS(s)-11	5′ - CGG AAA ACG TCA AAT AGT CC - 3′
AS(s)-12	5′ - CAG TCA GTA CGA GAA GTC GG - 3′
AS(s)-13	5′ - AGG TTG AGC AGG TAG ATG TC - 3′
AS(s)-14	5′ - ACA GGT CAG AGA TGG CCA GG - 3′
AS(s)-15	5′ - GGG GAC AGT AAG AAG GAA AA - 3′
AS(s)-16	5′ - GCA TAG TGA GCC CAG AAG GG - 3′
AS(s)-17	5′ - AGT CCC AGT GGG CGG CAG CA - 3′
AS(s)-18	5′ - ACA CAT TGT ATT TCC AAA GT - 3′
AS(s)-19	5′ - AGC CCT GTC AAG AGT TGA CA - 3′
AS(s)-20	5′ - AGA AGC CTA TAA AAT AGA GA - 3′
AS(s)-21	5′ - GAA GAA GAT TCC AGA GAA GA - 3′
AS(s)-22	5′ - ATT GTC AGG AGG TAG ATG AA - 3′
AS(s)-23	5′ - CAG CCA GGT ACC TAT CGA TT - 3′
AS(s)-24	5′ - CAC AGC ATG GAC GAC AGT CA - 3′
AS(s)-25	5′ - CTG GAT TTT AAA GCA AAC AC - 3′
AS(s)-26	5′ - CCC CAA AGG TGA CCG TCC TG - 3′
AS(s)-27	5′ - GAT CAC ACT TGT CAC CAC CC - 3′
AS(s)-28	5′ - ACA GCC ACC ACC GAA GTG AT - 3′
AS(s)-29	5′ - CTG GGA GAG GAG ACG CAA AC - 3′
AS(s)-30	5′ - TCT GGT AAA GAT GTA TCC TG - 3′

[Drawing 2]

AS(s)-31	5′ - AGA CCT TCT TTT TGA GAT CT - 3′
AS(s)-32	5′ - AGC TGC AGG TGT AAT GAA GA - 3′
AS(s)-33	5′ - ACT GTA TGG AAA ATG AGA GC - 3′
AS(s)-34	5′ - TTC CAG AAT TGA TAC TGA CT - 3′
AS(s)-35	5′ - TTA ATG TCT GGA AAT TCT TC - 3′
AS(s)-36	5′ - CCC CAA GAT GAC TAT CTT TA - 3′
AS(s)-37	5′ - AGC AGC GGC AGG ACC AGC CC - 3′
AS(s)-38	5′ - AGC AGA TGA CCA TGA CAA GC - 3′
AS(s)-39	5′ - TTT TAG GAT TCC CGA GTA GA - 3′
AS(s)-40	5′ - CGA CAC CGA AGC AGA GTT TT - 3′
AS(s)-41	5′ - GCC TCT TCT TCT CAT TTC GA - 3′
AS(s)-42	5′ - AAG CCT CAC AGC CCT GTG CC - 3′
AS(s)-43	5′ - AAT CAT GAT GGT GAA GAT AA - 3′
AS(s)-44	5′ - AGA AGA GAA AAT AAA CAA TC - 3′
AS(s)-45	5′ - AAT GTT GTA GGG AGC CCA GA - 3′
AS(s)-46	5′ - GTG TTC AGG AGA AGG ACA AT - 3′
AS(s)-47	5′ - CCA AAG AAT TCC TGG AAG GT - 3′
AS(s)-48	5′ - TCC AAC CTG TTA GAG CTA CT - 3′
AS(s)-49	5′ - TCC AAC CTG TTA GAG CTA CT - 3′
AS(s)-50	5′ - TCA CCT GCA TAG CTT GGT CC - 3′
AS(s)-51	5′ - CAT CCC AAG AGT CAC TGT CA - 3′
AS(s)-52	5′ - TTG ATG CAG CAG TGC GTC AT - 3′
AS(s)-53	5′ - AGG CAT AGA TGA TGG GGT TG - 3′
AS(s)-54	5′ - GAA CTT CTC CCC GAC AAA GG - 3′
AS(s)-55	5′ - ACT AAG AGG TAC TTT CTG AA - 3′
AS(s)-56	5′ - TGT GCT TTT GGA AGA AGA CT - 3′
AS(s)-57	5′ - GAA GCG TTT GGC AAT GTG CT - 3′
AS(s)-58	5′ - AAA ATA GAA CAG CAT TTG CA - 3′
AS(s)-59	5′ - CGG GAG CCT CTT GCT GGA AA - 3′
AS(s)-60	5′ - AAC TGA GCT TGC TCG CTC GG - 3′
AS(s)-61	5′ - CCA GTG GAT CGG GTG TAA AC - 3′
AS(s)-62	5′ - CAG ATA TTT CCT GCT CCC CA - 3′
AS(s)-63	5′ - TCC GTG TCA CAA GCC CAC AG - 3′

[Drawing 3]

AS(●)-64	5'-ATGGAGGGGATCAGTATATA-3'
AS(●)-65	5'-ATACACTTCAGATAACTACA-3'
AS(●)-66	5'-ACACCGAGGAAATGGGCTCA-3'
AS(●)-67	5'-TCAGGGGACTATGACTCCAT-3'
AS(●)-68	5'-CATGAAGGAACCCTGTTTCC-3'
AS(●)-69	5'-TCCGTGAAGAAAATGCTAAT-3'
AS(●)-70	5'-AATTTCAATAAAATCTTCCT-3'
AS(●)-71	5'-CCTGCCCACCATCTACTCCA-3'
AS(●)-72	5'-CCATCATCTTCTTAACTGGC-3'
AS(●)-73	5'-GGCATTGTGGGCAATGGATT-3'
AS(●)-74	5'-ATTGGTCATCCTGGTCATGG-3'
AS(●)-75	5'-TGGGTTACCAGAAGAAACTG-3'
AS(●)-76	5'-CTGAGAAGCATGACGGACAA-3'
AS(●)-77	5'-CAAGTACAGGCTGCACCTGT-3'
AS(●)-78	5'-TGTCAGTGGCCGACCTCCTC-3'
AS(●)-79	5'-CTCTTTGTCATCACCCTTCC-3'
AS(●)-80	5'-TCCCTTCTGGGCAGTTGATG-3'
AS(●)-81	5'-ATGCCGTGGCAAACTGGTAC-3'
AS(●)-82	5'-TACTTTGGGAACTTCCTATG-3'
AS(●)-83	5'-ATGCAAGGCAGTCCATGTCA-3'
AS(●)-84	5'-TCATCTACACAGTCAACCTC-3'
AS(●)-85	5'-CTCTACAGCAGTGTCCTCAT-3'
AS(●)-86	5'-CATCCTGGCCTTCATCAGTC-3'
AS(●)-87	5'-GTCTGGACCGCTACCTGGCC-3'
AS(●)-88	5'-GCCATCGTCCACGCCACCAA-3'
AS(●)-89	5'-CAACAGTCAGAGGCCAAGGA-3'
AS(●)-90	5'-GGAAGCTGTTGGCTGAAAAG-3'
AS(●)-91	5'-AAGGTGGTCTATGTTGGCGT-3'
AS(●)-92	5'-CGTCTGGATCCCTGCCCTCC-3'
AS(●)-93	5'-TCCTGCTGACTATTCCCGAC-3'

[Drawing 4]

AS(s)-94	5'-GACTTCATCTTTGCCAACGT-3'
AS(s)-95	5'-CGTCAGTGAGGCAGATGACA-3'
AS(s)-96	5'-ACAGATATATCTGTGACCGC-3'
AS(s)-97	5'-CGCTTCTACCCCAATGACTT-3'
AS(s)-98	5'-CTTGTTGGCTGCCTTACTAC-3'
AS(s)-99	5'-TACATTGGGATCAGCATCGA-3'
AS(s)-100	5'-CGACTCCTTCATCCTCCTGG-3'
AS(s)-101	5'-TGGAAATCATCAAGCAAGGG-3'
AS(s)-102	5'-GGGTGTGAGTTTGAGAACAC-3'
AS(s)-103	5'-CACTGTGCACAAGTGGATTT-3'
AS(s)-104	5'-TTTCCATCACCGAGGCCCTA-3'
AS(s)-105	5'-CTAGCTTTCTTCCACTGTTG-3'
AS(s)-106	5'-TTGTCTGAACCCCATCCTCT-3'
AS(s)-107	5'-TCTATGCTTTCCTTGGAGCC-3'
AS(s)-108	5'-GCCAAATTTAAAACCTCTGC-3'
AS(s)-109	5'-TGCCCAGCACGCACTCACCT-3'
AS(s)-110	5'-CCTCTGTGAGCAGAGGGTCC-3'
AS(s)-111	5'-TCCAGCCTCAAGATCCTCTC-3'
AS(s)-112	5'-CTCCAAAGGAAAGCGAGGTG-3'
AS(s)-113	5'-GTGGACATTCATCTGTTTCC-3'
AS(s)-114	5'-TCCACTGAGTCTGAGTCTTC-3'
AS(s)-115	5'-TTCAGCCTCAAGATCCTCTC-3'
AS(s)-116	5'-CTCCAAAGGAAAGCGAGGTG-3'
AS(s)-117	5'-GTGGACATTCATCTGTTTCC-3'
AS(s)-118	5'-TCCACTGAGTCTGAGTCTTC-3'
AS(s)-119	5'-TTCAAGTTTTCACTCCAGCTAA-3'

[Translation done.]